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14. ABSTRACT

The overall goal of this work was to design, implement, and characterize a novel dedicated mammotomography system for enhanced lesion detection. This novel system allows fully 3-D imaging of a pendant, uncompressed breast using novel 3-D complex orbit capabilities. A prototype system has been designed, developed, and extensively characterized with a number of figures of merit including SNR, dose efficiency, and contrast sensitivity. Results indicate the potential for sub dual-view dose uncompressed breast imaging. Observer studies have been performed to determine the lower limits of detectibility. Patient bed optimization has also been performed as well as system/bed positioning and tilt angles for optimal chest wall imaging and patient comfort. The outcome of this project is a fully functioning 3D dedicated breast imaging system ready for initial patient studies. In addition, the training provided by this grant has allowed the PI to continue on with further research and development of this system through SBIR and North Carolina state funding with the goal of commercialization.

15. SUBJECT TERMS

Dedicated Tomographic Breast Imaging, X-Ray Imaging, Computed Tomography

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Introduction

In the USA, breast cancer in women is one of the leading causes of malignancy and the second leading cause of death due to cancer (after lung cancer); in addition, from 2000 – 2004, its incidence rose at about 4% per year.[1] Thus, early detection of a primary cancer is of paramount importance, because treatment of a small tumor allows for more limited surgery with breast conservation and significantly reduces morbidity and mortality. Limitations in mammography have led to the progressive emergence of complementary imaging techniques. The dedicated breast Computed mammoTomography (CmT) solution we are proposing[2-10] has several potential benefits, including: (1) improved detection and characterization of breast lesions, especially in radiographically dense breasts,[2,11-13] through the removal of contrast-reducing overlying tissue; (2) *uncompressed* breast imaging for greater patient comfort with an associated potential increase in participation rates; (3) breast dose equal to or less than that of current dual view mammography with anticipated increased image contrast; and (4) expectedly improved positive predictive value, especially for radiographically dense breasts. The main goal of this work was to design, develop, implement, and characterize a novel, dedicated computed mammotomography system using cone-beam imaging geometry, having novel degrees of freedom of movement with a unique offset geometry, and using iterative reconstruction techniques. Such a system has been successfully designed and developed and is now entering the patient trial phase. In addition, a company has been founded to commercialize this technology with the PI of this grant becoming the CEO. It is hoped that this research and development will ultimately lead to a commercial system capable of *in vivo* tissue differentiation resulting in an improvement in the detection and diagnosis of breast cancer.

Body

In the first year of the study, Task 1 (a) through (e) and Task 3(c) were completed in their entirety. These tasks consisted primarily of design, develop, and construction of a fully automated and synchronized dedicated 3D breast imaging system, optimization of various correction algorithms including gain, offset, and defective pixel, and development of unique offset half-cone beam orbits for maximization of the range of uncompressed breast sizes that could be accommodated. Task 3(c) involved determination of normalized glandular dose coefficients for our uncompressed breast acquisitions. A detailed summary of progress on these tasks can be found in the Year 1 Annual Report. The Year 2 Report summarizes successful research efforts for Tasks 2(a), 2(c), 3(a), and 3(b). Tasks 2(a) was comprised of work primarily designed to investigate the use of unique 3D cone-beam orientations and tilt angles to maximize chest wall proximity imaging. In conjunction with optimized cone-beam orientations, Task 3(c) investigated optimization of the patient bed to further allow chest wall proximity imaging as well as provide patient comfort. Tasks 3(a) and 3(b) involved evaluation of system performance in terms of a number of figures of merit including SNR, dose, dose efficiency, contrast sensitivity, and detection threshold limits through the use of observer studies. The final year of the grant involved further work on Tasks 3(a) and 3(b) as well as investigation of feasibility of patient bed motion during the acquisition (Task 2b).

As was noted in the Year 2 report, it should once again be mentioned that several of the studies completed for this proposal were done in conjunction with other junior members of the Multi-Modality Imaging Laboratory, some of whom became first authors on the appropriate conference proceeding. This was done to give more junior members an opportunity to share in the studies as a learning experience as well as provide the opportunity to the author to practice skills in guiding junior members of the lab. Specific Year 3 sub-task details and progress are provided below. Some of this time was also spent providing guidance to the team for integration and development of the

first dedicated dual-modality SPECT/CT breast imaging system. Although not directly related to the goals of this grant, the author also participated in initial patient studies with the completed dual-modality system. This was made possible through the development of the system provided by this grant and was funded by the R01 grant of the lab director. Some of the resulting data is included in the appendix for interest and completeness.

Task 3(a). This subtask was to evaluate different breast sizes, compositions, lesion sizes, microcalcifications to determine upper and lower detection limits as well as effect on breast volume sampling. The Year 2 report outlines results addressing the bulk of the research goals of this Task.

Some work was carried out (see Year 1 report) with microcalcifications in our initial simulations. In addition, it was determined from our contrast observer studies (Year 2 report) that high contrast objects in the absence of background could be visualized equally or better with mammography. It is also accepted in the scientific community that microcalcification detection will likely remain best with mammography as compared to other modalities. Because of these factors, it was decided to not pursue further experimentation with microcalcifications at this point but rather, to continue focusing on the more difficult problem of soft tissue differentiation, especially in dense breasts.

To that end, the remainder of effort for Task 3(a) was directed toward further evaluation of breast sizes with respect to the ability to get close to the chest wall, given the limitations of our current geometry and bed design and given the integration of the system into a dual-modality mode.

With a fixed tilt required by the current dual modality imaging configuration, we are still unable to get the full breast up to and including the chest wall. Approximately 1-2cm from the chest wall into the breast is still missing. Further bed modifications will be required in addition to acquisition of a detector and x-ray tube with significantly reduced dead zones. These improvements have been proposed in subsequent grant applications.

Task 3(b). This sub-task was to evaluate system and acquisition methodologies for effects on image quality including signal to noise ratio, dose efficiency, contrast sensitivity, resolution metrics (2D and 3D MTF, NPS, DQE), artifacts, and attenuation coefficient (quantitation) accuracy. The Year 2 report outlines results addressing the bulk of the research goals of this Task. Additional work remained in the areas of attenuation coefficient accuracy and artifacts.

Effort was focused on the removal of artifacts associated with the offset geometry being used by the present system. It was determined through Monte Carlo simulations that remaining artifacts were largely due to the fact that we used an offset geometry. The offset geometry was originally deemed necessary due to the small size of the existing detector together with the range of breast sizes and image magnification expected. Without offset, we would not be able to image breasts larger than 15cm diameter. Ultimately, the optimal solution would be to use a detector large enough to accommodate the largest breasts in a centered geometry (e.g. the Varian 4030). However, in the near term, it was necessary to determine ways to reduce the present artifact. It was found that, rather than try to design the equipment to minimize overlap, with the risk of missing the central part of the breast and perhaps the periphery, the better interim solution was to eliminate the overlap in software by cropping the raw images prior to processing the input deck for reconstruction. As can be seen in Figure 1 below, the post-cropped reconstruction (bottom row, right) has eliminated much of the artifacts as compared to the pre-cropped reconstruction (bottom row, left).

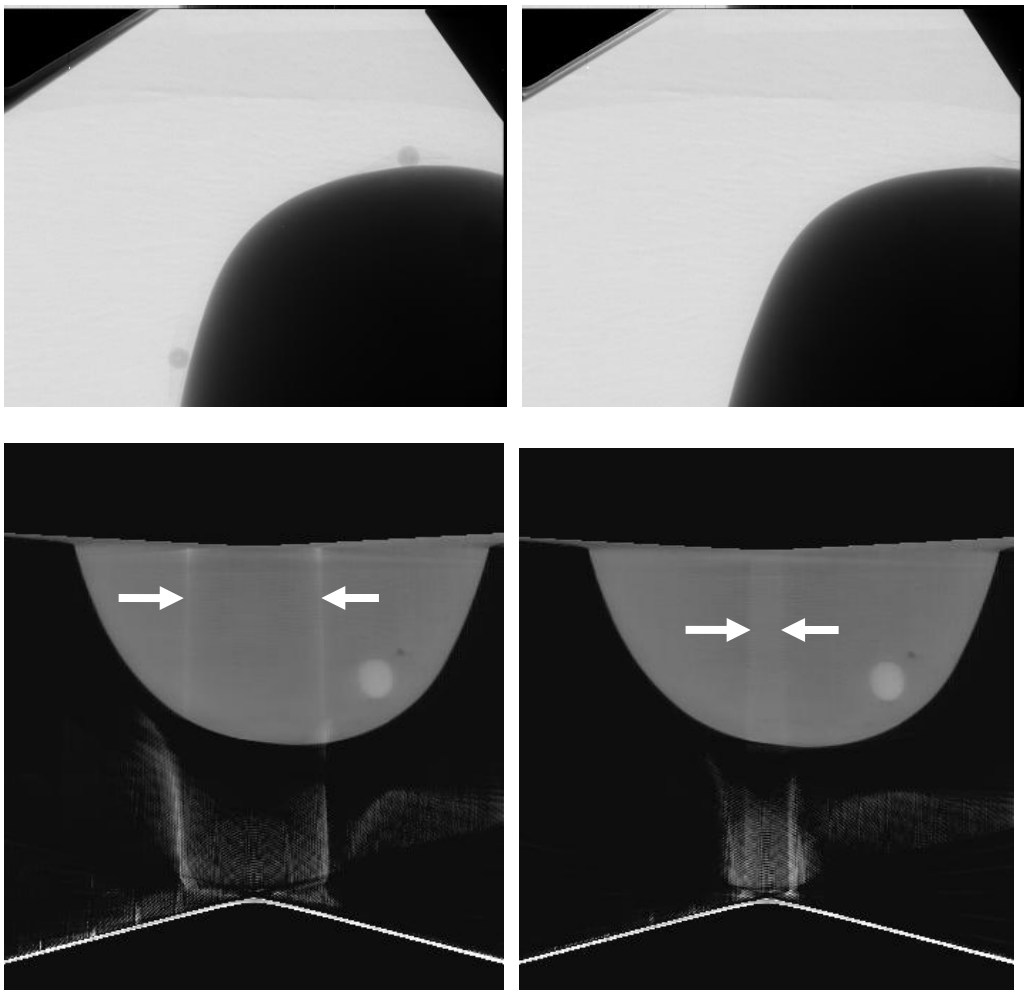

Figure 1 (Top Row) Uncropped (Left) and cropped (Right) projection images and (Bottom Row) corresponding reconstruction for (Left) uncropped and (Right) cropped images. Note how the artifact area within the vertical lines (white arrows) has been significantly reduced. (thanks to Priti Madhav for these images)

Attenuation coefficient investigations have indicated that results are within 2 % of actual attenuation coefficients (estimated from NIST tables and calculated mean beam energies) for small breasts and 7% for large breasts (Table 1). The difference in accuracy can be accounted for by significant differences in x-ray scatter, with more scatter in larger breasts causing greater inaccuracy. While 2-7% accuracy is encouraging, it is apparent that scatter correction techniques will be required if we wish to use absolute attenuation coefficients for tissue differentiation in the future.

Table 1. Attenuation coefficient results for small and large breasts. Theoretical water attenuation coefficient was determined from mean energy (36.4 keV) of simulated spectra, using cubic spline interpolated NIST data.

	Measured μ center (cm^{-1})	**Measured μ edge (cm^{-1})**	**Theoretical μ (cm^{-1})**	**Coefficient Error**
Small Breast	0.2515	0.2737	0.2789	1.9%
Large Breast	0.2042	0.1043-0.2590	0.2789	7.2

Task 2(b). This sub-task was to evaluate feasibility of utilization of patient bed motion versus camera system motion to provide vertical displacements *during* a scan at specific azimuthal and polar acquisition angles, to circumvent the physical limitations of the patient's torso by exploiting the unhindered spaces along the sides of the patient.

Initial investigations into patient bed movement during acquisition exposed serious difficulties with this approach in terms of feasibility. The major issue encountered was the lack of repeatable and precise movement of the patient bed. It will be necessary to develop a more precise patient bed motion and/or develop a vertical motion on the system itself for movement of the system vertically while keeping the patient and bed still. This will have the added benefit of removing the potential for patient motion during vertical bed motion. In addition, dimensions of the current bed and SID do not allow for lowering the bed significantly into the field of view. A narrower bed is warranted. Given that funds were not available for this development, efforts were redirected into other approaches for getting closer to the chest wall.

Partial angle investigations (Figure 2) indicated that with offset geometry, the partial angle scan approach is not feasible (Figures 3 and 4). Further partial angle investigations will need to be done with the system centered and with a larger detector.

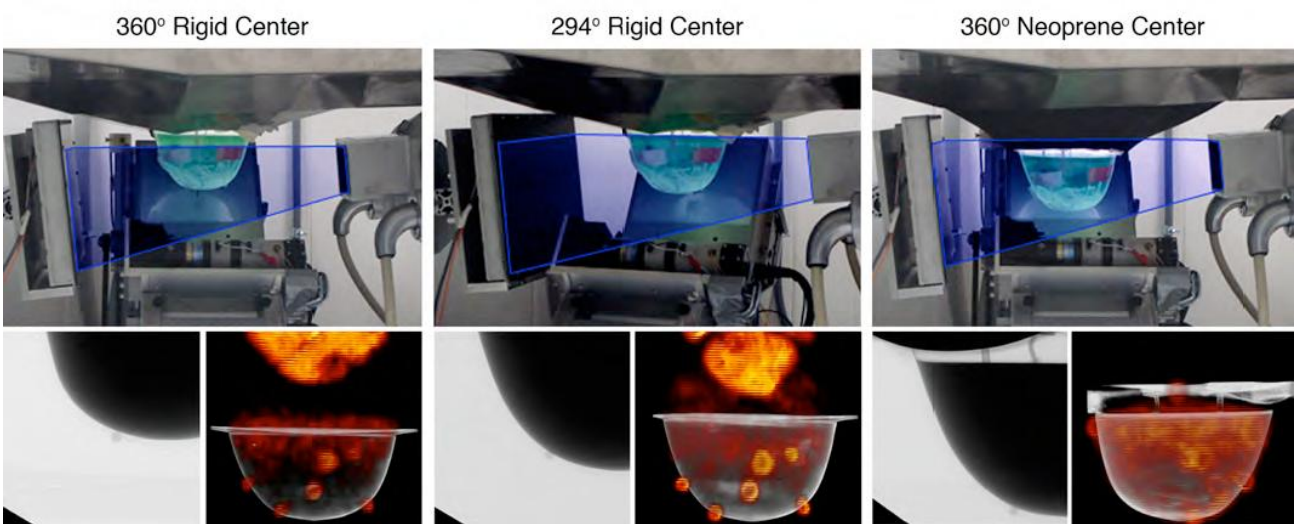

Figure 2. Breast phantom positioned (Top Left) with bed high enough for 360º clearance, (Top Middle) with bed lowered to 294º reduced angle scan, and (Top Right) with flexible center and 360º clearance. Estimated CT cone-beam FOVs are illustrated in blue. Corresponding CT projection data and reconstructed, fused SPECT-CT volume renderings are shown below each system photo. Yellow arrow in bottom center highlights the 3.5mm lesion not seen in the rigid center 360º scan at left. There was no heart activity used in this neoprene study. (thanks to Spencer Cutler for this figure and caption)

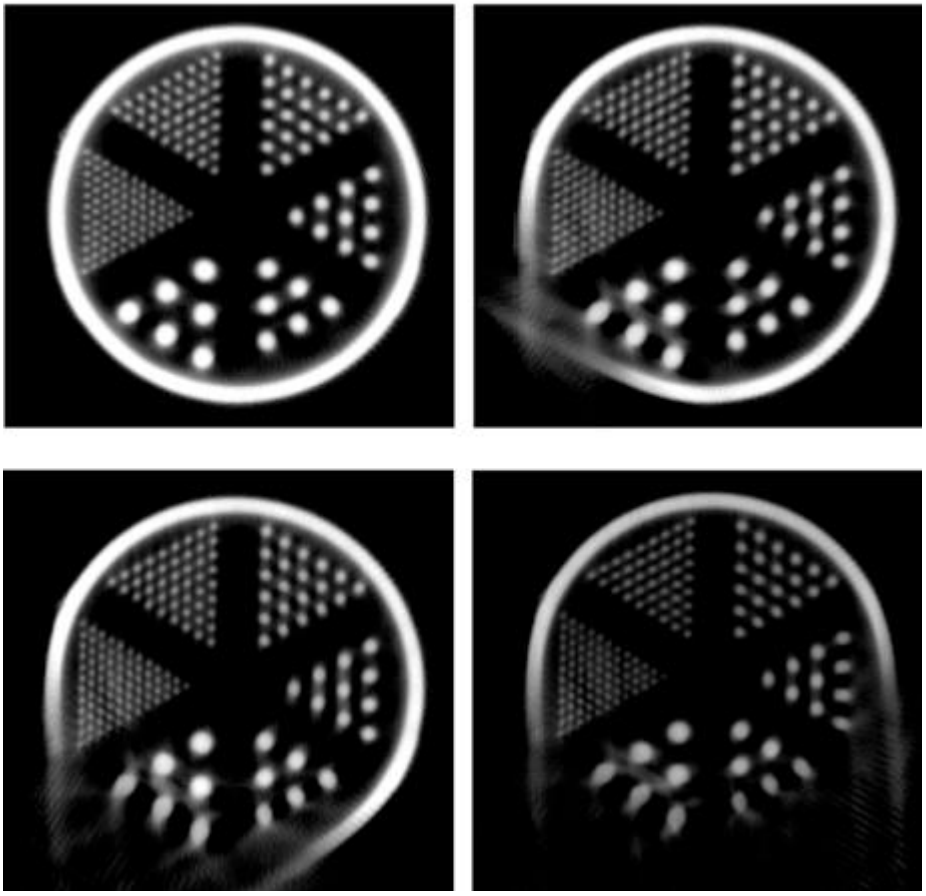

Figure 3. OSTR Reconstructed CT cold rod data acquired with the central cone-beam ray offset 5cm from the COR. Scan angles are (Top Left) 360°, (Top Right) 300°, (Bottom Left 240°, and (Bottom Right) 180°. Data insufficiency artifacts become more apparent with decreasing angular sampling. (thanks to Spencer Cutler for this figure and caption)

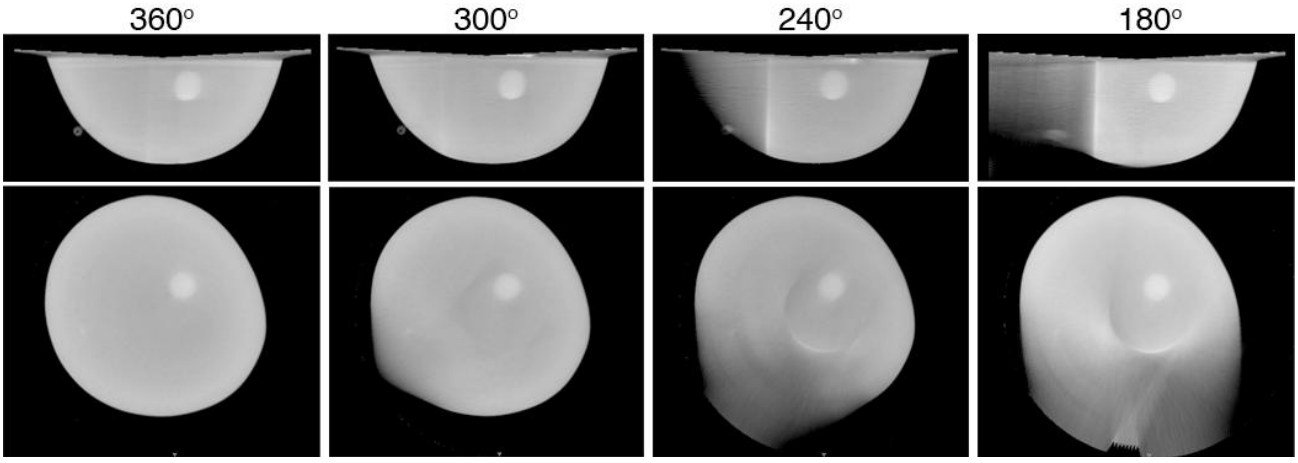

Figure 4. Reconstructed CT sagittal (Top) and coronal (Bottom) slices. The complete 360° data are compared with reduced angle scans using 300°, 240°, and 180° of angular sampling. The central cone-beam ray was laterally offset 5cm resulting in truncation artifacts seen in the areas where projection views were not collected. (thanks to Spencer Cutler for this figure and caption)

Further studies will be necessary to understand better the trade-off between distortions created by fixed angle acquisitions (and subsequent failure to meet Tuy's data sufficiency condition), patient

comfort issues with a narrower bed, and implications on flux and thick filter quasi-monochromatic beams created by larger SIDs that may be required for getting closer to the chest wall.

Key Research Accomplishments

Summary:
All tasks have been completed. The Year 1 and Year 2 reports provide details on what was accomplished for each of these periods. Year 3 has been detailed above. Sub tasks were completed in their entirety with the exception of vertical bed motion and detailed microcalcification experimentation, for the reasons mentioned previously.

Accomplishments:

1. We have successfully implemented the world's first dedicated tomographic breast imaging device that is capable of complex orbits.
2. The complex orbit capability allows this device to be the only current cone-beam breast imaging device capable of satisfying Tuy's data sufficiency condition, thereby eliminating cone-beam distortion artifacts.
3. This complex orbit capability will also allow us to image close to the chest wall than other devices.
4. Initial dose studies indicate that we may do full breast scans at $1/10^{th}$ the dose of dual view mammography. This is the only such device with this capability.
5. We continue to evaluate and improve the world's first dedicated tomographic breast imaging device that is capable of 3-dimensionally complex orbits.
6. We have performed the first ever observer study comparing mammotomography and FFDM using realistic breast phantoms and have shown mammotomography to have significant advantages over FFDM, especially for dense breasts.
7. We have designed, developed, and produced a custom bed that will allow imaging closer to the chest wall, the last major challenge of dedicated breast CT.
8. Observer studies have confirmed that we can image at doses lower than dual view mammography while maintaining the ability to detect sub-cm lesions in a dense background.
9. Results indicate the potential for absolute attenuation coefficient differentiation of lesions, though further work is required for artifact and scatter correction.
10. Partial angle sampling in order to capture more of the breast close to the chest wall is not feasible with offset geometry but may be an option with a centered geometry. Further refinement of the patient bed is also required.
11. The CmT system has been incorporated into the world's first dual-modality SPECT/CT dedicated breast imaging system.

Reportable Outcomes

Peer reviewed – in preparation:

DJ Crotty, CN Brzymialkiewicz, **RL McKinley**, MP Tornai. "Quantifying Transmission Source Contamination of the Emission Image in a Common Field-of-View Dual Modality SPECT-CT Mammotomography System." *IEEE Trans. Nucl. Sci*. (Submitted 09/2006; In Revision 05/2007).
P Madhav, **RL McKinley**, E Samei, JE Bowsher, MP Tornai. "A Novel Method to Characterize the MTF in 3D for Computed Mammotomography." In preparation for *Medical Physics.*

RL McKinley, MP Tornai, E Samei. "An Observer Study Comparison of Computed Mammotomography and Digital Mammography." In preparation for *Medical Physics.*

RL McKinley, MP Tornai, P Madhav, SJ Cutler, DJ Crotty, E Samei. "Design and Development of a Fully-3D Dedicated X-Ray Computed Mammotomography System." In preparation for *Phys. Med. Biol.*

Conference Proceedings and Abstracts:

P Madhav, DJ Crotty, SJ Cutler, **RL McKinley**, MP Tornai. "A Novel Dual-Modality SPECT-CT Dedicated System for 3D Volumetric Breast Imaging." Presented at *Seeing is Believing: The Future of Molecular and Biomolecular Imaging*, Duke University, Durham, NC, 11-13 March, 2007, and *Duke Frontiers 2007*, Duke University, Durham, NC, 14 May, 2007.

M Tornai, P Madhav, D Crotty, S Cutler, **R McKinley**, K Perez, J Bowsher. "Initial hybrid SPECT-CT system for dedicated fully-3D breast imaging." Presented at *The Society of Nucl. Med. 54th Annual Meeting*, Washington, DC, 2-6 June 2007, and published in *J. Nucl. Med*. **48**(5). 2007.

MP Tornai, P Madhav, DJ Crotty, SJ Cutler, KL Perez, **RL McKinley**, JE Bowsher. "Application of volumetric molecular breast imaging with a dedicated SPECT-CT mammotomograph." Presented at the *49th Annual Meeting of the American Association of Physicists in Medicine*, Minneapolis, MN, 22-26 July 2007, and published in *Med. Phys.* **34**(6):2597.

R McKinley, M Tornai. "Development and characterization of a dedicated computed mammotomography system." Submitted to the *2008 DOD Era of Hope Conference on Breast Cancer*.

DJ Crotty, P Madhav, SJ Cutler, KL Perez, **RL McKinley**, MP Tornai. "Development of an Integrated SPECT-CT Imaging System for Enhanced Dual-Modality, Dedicated Breast Imaging." Presented at *Duke University BME Annual Research Retreat*, 7-9 October, 2007, Myrtle Beach, SC.

P Madhav, SJ Cutler, DJ Crotty, KL Perez, **RL McKinley**, MP Tornai. "3D Volumetric Breast Imaging with a Dedicated Dual-Modality SPECT-CT System." Presented at *Duke University BME Annual Research Retreat*, 7-9 October, 2007, Myrtle Beach, SC.

Additional Funding Received Post Award:

Principal Investigator: "Overcoming limitations of breast volume imaging in 3D dedicated mammotomography." Zumatek, Inc., Chapel Hill, NC 27514. Source: National Institutes of Health - National Cancer Institute SBIR Phase I, 1R43CA125924-01 (Funded; Period = 9/2007 – 9/2008; Amount = $100,000).

Principal Investigator: "Overcoming limitations of breast volume imaging in 3D dedicated mammotomography." Zumatek, Inc., Chapel Hill, NC 27514. Source: North Carolina Board of Science and Technology Matching Funds SBIR Phase I, 2088464 (Funded; Period = 1/2008 – 1/2009; Amount = $100,000).

Other:

- Company founded for commercialization of the technology
- SBIR and state matching funds received for commercialization of the technology

- Duke spin-out company providing full employment of PI
- Technology chosen by Prevention Magazine (Jan 2008) and Readers Digest (Mar 2008) as one of the top medical breakthroughs for 2008.

Conclusions

With our fully synchronized and automated system capable of complex orbits, measurements and observer studies have indicated that we can perform mammotomography scans at a fraction of the dose of dual view mammography and that mammotomography significantly outperforms FFDM through the removal of overlying structure and is most significant in dense breasts. A prototype bed has been designed and developed and is ready for further phantom evaluation and eventual patient scanning (outside the present scope of the grant). This system shows high promise as a diagnostic tool for women having suspicious mammograms, especially those with dense breasts. Ultimately, it may replace current standard mammography. Chest wall proximity imaging remains the last major hurdle to overcome before clinical introduction of this scanner.

Development of this system has proven to be worthwhile scientifically, clinically, and professionally. Many scientifically significant outcomes have resulted from this funding and a device ready for clinical trials has shown initial promise of improving detectability of lesions, ultimately leading to increased survival. Professionally, the funding has provided a substantial depth and breadth of experience. It has also resulted in the formation of a company, successful initial funding for the commercialization effort, and full time employment of the PI.

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Appendices

Appendix A

STATEMENT OF WORK

Task 1 Implement prototype system for unique acquisition capabilities (Months 1-12)

a. Implement mounting system for X-ray source and detector for flexible acquisitions involving azimuthal rotation and polar tilt (Months 1-2)
b. Automate data acquisition sequence, synchronizing detector readout in software with gantry control and generator exposure initiation (Months 2-3)
c. Perform initial phantom measurements using Catphan and other 3D geometric frequency/resolution phantoms to optimize cone-beam reconstruction, utilizing ordered subsets based iterative transmission reconstruction techniques for 3D cone-beam acquisition (Months 4-6)
d. Using simple acquisition geometries, optimize image gain, offset, and line correction algorithms to maximize projection image quality and noise reduction (Months 5-7)
e. Design and evaluate offset half cone-beam using 360 degree acquisition as well as horizontal versus vertical positioning of detector for maximizing range of uncompressed breasts accommodated (Months 8-12)

Task 2 Design and evaluate unique acquisition geometries (Months 13-26)

a. Investigate unique 3D cone-beam orientations and tilt angles for optimal orientation relative to the longitudinally oriented patient chest wall (Months 13-18)
b. Evaluate feasibility of utilization of patient bed motion versus camera system motion to provide vertical displacements *during* a scan at specific azimuthal and polar acquisition angles, to circumvent the physical limitations of the patient's torso by exploiting the unhindered spaces along the sides of the patient (Months 19-23)
c. Modify patient bed materials and breast opening size as well as bed contour to maximize curvature (and comfort) of patient chest for full volumetric sampling, including chest wall (Months 23-26)

Task 3 Evaluate various breast sizes, compositions, lesion sizes, microcalcifications (Months 27-36)

a. Evaluate different breast sizes, compositions, lesion sizes, microcalcifications to determine upper and lower detection limits as well as effect on breast volume sampling (Months 27-31)
b. Evaluate system and acquisition methodologies for effects on image quality including signal to noise ratio, dose efficiency, contrast sensitivity, resolution metrics (2D and 3D MTF, NPS, DQE), artifacts, and attenuation coefficient (quantitation) accuracy (Months 32-36)
c. Determine normalized glandular dose coefficients for CmT acquisitions for dose determination in preparation for clinical trials (Months 32-36)

Appendix B

AAPM 2007 Annual Meeting – presented Minneapolis, July, 2007.

WE-D-L100J-08

Application of Volumetric Molecular Breast Imaging with a Dedicated SPECT-CT Mammotomograph

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Purpose: Clinical 2D-scintimammography therapeutic response monitoring results imply that fully-3D molecular imaging could benefit early response prediction. Capabilities of prototype functional SPECT and anatomical x-ray CT integrated imaging subsystems, dedicated to whole breast and chest wall diagnostic imaging of normalcy, disease and therapeutic response are demonstrated. The system provides patient comfort while imaging the pendant, uncompressed breast and anterior chest wall in common fields-ofview, yielding inherently registered, volumetric images.

Method and Materials: The high-performance SPECT system has 2.5mm CZT multielement pixelation and 6.7% FWHM energy resolution at 140keV; the subsystem gantry can sweep the camera about a hemisphere with simple/complex trajectories. The CT subsystem has 15% FWHM quasimonochromatic x-ray cone beam at 36keV and 127micron CsI microcolumnar pixelation. Both subsystems rotate on a common azimuthal stage. The CT system is equatorially restricted, though fully 3D positioning mobilization is possible for both subsystems on the same hybrid gantry. Emission SPECT data are iteratively reconstructed using OSEM, and transmission CT data using iterative OSTR. Rigid body transformations employing mixed emission/transmission fiducial markers around the breast help register and fuse the reconstructed data.

Results: Initial cross contamination studies indicated transmission scatter contamination of SPECT images was negligible (<1%). Emission contamination of CT images was greater, degrading reconstructed image SNR by 20-30%. Use of a radio-opaque patient bed reduces emission contamination. Registered and fused data yield high-resolution images of geometrical and anthropomorphicphantoms. New designs of the fully flexible hybrid system will allow for nearly complete sampling by both subsystems.

Conclusion: A hybrid SPECT-CT mammotomography system was successfully implemented for use in breast diagnostics.

Conflict of Interest: MPT and JEB are inventors of this technology, and are named as inventors on the patent for this technology applied for by Duke. If this technology becomes commercially successful, they and Duke could benefit financially.

Appendix C

Duke Cancer Center 2008 Annual Meeting – 2 abstracts submitted.

Category: Clinical Science
Submitting Author: Priti Madhav, M.B., M.S.
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Dedicated Molecular and Anatomical Breast Imaging - Initial Patient Studies

Priti Madhav, Spencer Cutler, Dominic Crotty, Kristy Perez, Randolph McKinley, Kelly Marcom, Terence Wong, Martin Tornai

Breast cancer is the most commonly diagnosed cancer among women worldwide and is the second leading cause of cancer death in the US. With the limitations and discomfort of mammography, alternative imaging techniques to detect and monitor breast cancer early, reduce unnecessary biopsies, and improve patient comfort have been designed. We have developed a compact, dedicated, dual-modality SPECT (single photon emission computed tomography - a molecular imaging approach) and CT (computed tomography - a diagnostic imaging approach) system, which allows for quantitative 3D volumetric functional and anatomical imaging, respectively, of a pendant, uncompressed breast. Fused images can potentially provide more valuable clinical information for evaluation of cancerous diseases than the independent systems alone. A preliminary investigation on the clinical performance of the hybrid system was done by imaging women with biopsy confirmed breast cancer. With no breast compression and an open, common field-of-view geometry system, the patient lies prone on a customized patient bed while the hybrid device non-invasively acquires 3D data underneath. Using the flexible positioning capability of the gantry, the SPECT subsystem acquires data using a 3D complex trajectory, which permits the camera to get closer to the breast and chest wall. CT images were collected with the system rotating circularly around the breast. Initial human subject studies demonstrated that SPECT images can clearly visualize the tracer uptake by the tumor, and the subsystem has the capability to view into the chest wall. Physical system constraints limited visualization of the chest wall in the CT images. With the elimination of overlapping tissues through 3D imaging, CT images can potentially improve lesion isolation versus conventional screening modalities. Future studies include improved patient positioning for better CT chest inclusion as well as clinical comparisons with mammograms and/or MRI images for quantification of potential improved detection.

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Performance of a New Dual-Modality Molecular-Anatomical Imaging System Dedicated to Breast Imaging

Dominic Crotty, Priti Madhav, Spencer Cutler, Kristy Perez,
Randolph McKinley, Martin Tornai

Dual-modality tomographic systems dedicated to breast imaging offer great promise in the detection and characterization of primary, recurrent and occult cancers, and monitoring chemo and radiation therapies. Sequential acquisition with dedicated molecular (SPECT) and anatomical (x-ray CT) 3D volumetric imaging systems can aid in visualizing tumors by using the anatomical structure and characterizing the molecular activity by quantifying the radioactive uptake from the images. Dual modality systems additionally enable improved SPECT image quantification and quality arising from the use of reconstructed CT data to correct for attenuation of the emitted photons. An integrated imaging system with a common field-of-view is expected to further enhance the visual and quantitative information over independent systems, as well as decrease patient imaging time. Thus, SPECT and CT imaging systems were independently developed in our lab and have since been combined onto a common gantry. The fully-3D SPECT subsystem permits complex acquisition trajectories around the uncompressed breast to avoid physical hindrances, overcome distortions due to inadequate sampling, and allow detection of lesions on the chest wall. The CT subsystem, restricted to circular rotation, has an offset geometry to allow imaging wide range of breast sizes. For full computed tomography of the breast, the quasi-monochromatic cone-beam x-ray source allows for reduced radiation dose as compared to standard dual-view mammography and additionally improves image contrast between soft tissues with similar attenuation coefficients. Here, we provide an overview of the prototype integrated SPECT-CT system, complete with a novel custom-designed patient bed. System capabilities, including data sampling, resolution and image fusion are demonstrated with geometric and anthropomorphic breast phantom measurements using fiducial markers.

Appendix D

IEEE Medical Imaging Conference 2007

Initial Patient Study with Dedicated Dual-Modality SPECT-CT Mammotomography

Priti Madhav, *Member, IEEE*, Spencer J. Cutler, *Member, IEEE*, Kristy L. Perez, *Member, IEEE*, Dominic J. Crotty, *Member, IEEE*, Randolph L. McKinley, *Member, IEEE*, Terence Z. Wong, Martin P. Tornai, *Senior Member, IEEE*

***Abstract*– Dual-modality SPECT-CT dedicated breast imaging offers great promise in the detection/staging of cancer and the monitoring of treatment therapies. The sequential acquisition with emission (nuclear) and transmission (x-ray) 3D imaging systems can aid in localizing the radioactive uptake of a tumor from the emission image by using the anatomical structure from the transmission image as a roadmap. Both independent SPECT and CT subsystems are mounted onto a single gantry that rotates around the vertical axis of a pendant, uncompressed breast. To evaluate the feasibility of this dedicated system, geometric phantoms and breast phantoms using fiducial markers were acquired to study the sampling and resolution properties and demonstrate the fusion of the functional-anatomical images. In addition, a preliminary investigation on the clinical performance of the system was done by imaging two women with confirmed breast cancer: one on the independent SPECT system and the other on the SPECT-CT system. Further patient hybrid imaging studies are in progress. This compact dedicated SPECT-CT system is capable of non-invasively providing complementary functional and anatomical fully-3D activity distribution information of the breast, and has the potential to help further enhance the visual and quantitative information over the independent systems.**

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women worldwide and is the second leading cause of cancer death in the United States. However, because of technological advancements in early detection and better treatment options, breast cancer death rates have been dropping since 1990. With early detection, there is less chance of metastasis and the therapeutic treatment of smaller tumors can allow for limited surgery with breast conservation which can help minimize pain, suffering, and increased mortality. Currently, x-ray mammography is the most widely used screening procedure in the U.S., with reported high sensitivity and specificity [1]. However, its limitations including low image contrast, structural overlap, patient discomfort due to breast compression, and precise lesion localization have resulted in high false negative rates especially in younger women with denser breasts [2, 3].

These limitations have led to the emergence of fully-3D imaging approaches in magnetic resonance imaging [4], ultrasound [5], nuclear medicine [6, 7], and computed tomography (CT) [8-10] with the goal of improving detection of breast lesions, reducing unnecessary biopsies, and increasing patient comfort. Combined dual-modality systems have also been developed in order to merge complementary information from different modalities to advance patient care and improve diagnostic accuracy [11, 12]. Whole-body SPECT-CT systems have been shown to improve the localization of lymph nodes over planar imaging due to the improved quality of the SPECT images gained by attenuation correction and anatomic landmarks from the CT images [13, 14].

A hybrid scanner has recently been built in our lab for dedicated breast imaging by combining independently developed dedicated breast SPECT and CT technologies [11, 12]. The fully-3D motion capability of the SPECT system allows imaging closer to the breast. Additionally, the quasi-monochromatic nature of the x-ray cone-beam source allows for less radiation dose and increase in contrast between similar soft tissue attenuation coefficients. The sequential acquisition with emission and transmission systems will aid in the localization of the radioactive metabolic uptake of a tumor with the structural framework of an object.

MATERIALS & METHODS

The first prototype compact dual-modality system (Fig. 1) was built to image a pendant uncompressed breast. Both SPECT and CT sub-systems are secured to a common rotation stage (model RV350CCHL, *Newport Corp.*, Irvine, CA) to allow an azimuthal rotation of 360° around the vertical axis of the breast. The SPECT sub-system is fixed at 90°

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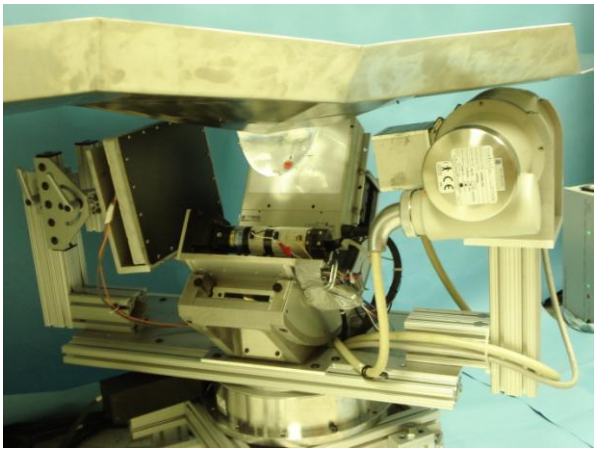

Fig 1: Photograph of the prototype dual-modality dedicated breast imaging tomographic system. The SPECT system (center) is placed orthogonally to the CT tube (right) and digital flat-panel detector (left). The bed is placed above the system with a breast phantom through the center opening in the table. Note that the breast phantom is in the common FOV of each system.

relative to the x-ray source-detector axis. A customized patient bed [15-17], positioned over the system, allows a woman to lie down in a prone position suspending one pendant breast through a hole to be scanned.

a. SPECT System

The SPECT system uses a compact 16x20cm^2 field of view Cadmium-Zinc-Telluride (CZT) *LumaGEM* 3200S^{TM} gamma camera (*Gamma Medica, Inc.*, Northridge, CA) with discretized crystals, each 2.3x2.3x5mm^3 on a 2.5mm pitch. The measured mean energy resolution of the gamma camera at 140keV is 6.7% FWHM (full-width-half-maximum) and collimator sensitivity is 37.9 cps/MBq. This system has a parallel-hole collimator with hexagonal holes (1.2mm hole size flat-to-flat (inner diameter), 0.2mm septa, and 25.4mm height). The camera is attached to a laboratory jack (model M-EL120, *Newport Corp.*, Irvine, CA) and a goniometric cradle (model BGM200PE, *Newport Corp.*, Irvine, CA) permitting various radius of rotations and 0° to 90° polar tilt angles, respectively. With this flexible gantry, the camera can be positioned anywhere in a hemisphere to facilitate acquiring projection data around a pendant, uncompressed breast [6, 18, 19]. Additionally, the small, high performance dedicated camera, can acquire images close to the breast, thereby minimizing spatial resolution degradation and reducing background contamination from other organs.

b. CT System

The CT system consists of a rotating tungsten target cone-beam x-ray source (model Rad-94, 0.4mm focal size, 14° anode angle) (*Varian Medical Systems*, Salt Lake City, UT) and CsI(T1)-based amorphous silicon digital x-ray detector (*Varian Medical Systems*, Salt Lake City, UT) with a grid size of 1920x1536 pixels and 127μpixels [10]. The source and detector are secured to a metal plate underneath the SPECT goniometer which is then attached to the azimuthal rotation stage. A filter is inserted into a custom built collimator attached to the x-ray source to produce a quasi-monochromatic x-ray source which can (1) improve the visualization of tissues with very small differences in attenuation coefficients [20]; (2) lower the x-ray dose [21]; and (3) minimize beam hardening [22, 23]. For these studies, a Ce 100th attenuating value layer (0.0508cm) filter (Z=58, ρ=6.77g/cm^3, K-edge=40.4keV, *Santoku America, Inc.*, Tolleson, AZ) was used to yield a mean energy of ~36keV and FWHM of 15%. Source-to-image distance (SID) used was 60cm and source-to-object distance (SOD) was 38.1cm resulting in a magnification of 1.57 for an object located at the system's center of rotation. The central ray of the CT cone beam is laterally offset 5cm relative to the center of rotation to completely sample the entire volume of interest [24]. Unlike the SPECT system, the CT system is at a fixed 6.2° tilt angle and restricted to only azimuthal motion.

c. Patient Bed

A customized patient bed, placed over the hybrid device, was built to allow for patient comfort and avoid collision with the imaging system (Fig. 1) [16]. It is comprised of stainless steel, along with a thin lead, neoprene, and polyurethane lining laid on top for patient protection from errant radiation and patient comfort. The lead shielding is used to prevent any contamination from the heart and other organs on the CT images. The bed is angled at the waist in order to support the patient and allow chest protrusion such that the maximal amount of breast volume can fit through the opening in the center which is over the common field of view (FOV) of both systems. The octagonal trough allows for system rotation underneath it, and a removable insert allows for radiolucent materials to be used for imaging up to and through the chest wall.

This bed is attached on top of a positioning system (model 830-058, *Biodex Medical Systems*, Shirley, NY) which can be displaced in five different directions to allow adjustment for any bowing that might occur due to the weight of the patient and permit the maximal breast volume in the field of view [17]. The head side of the bed is supported to minimize motion of the bed during acquisition.

d. Sampling and Resolution Properties

Using the integrated, prototype hybrid system, images were acquired with a mini-Defrise and mini-cold rod phantoms (*Data Spectrum Crop*. Hillsborough, NC) to study the sampling and resolution properties, respectively. Both phantoms were imaged on the hybrid gantry assembly, but the images were acquired separately: for CT, the phantoms were assembled without any interstitial material (air only), while for SPECT, the phantoms were removed from the FOV, filled with aqueous radioactivity, then scanned.

The mini-Defrise phantom consisted of five 5.0mm discs, spaced 5.0mm apart, in a cylinder with 70mm depth. For the SPECT measurements, 9mCi (333MBq) of aqueous ^{99m}Tc-pertechnetate was distributed between the five acrylic discs creating six "emission discs". In the mini-cold rod phantom, the rods in each of the six sectors have equal diameters of 4.7, 3.9, 3.1, 2.3, 1.5, and 1.1mm, spaced on twice their diameters. For the SPECT measurements, 9.5mCi (351MBq) of aqueous ^{99m}Tc-pertechnetate filled the spaces between the rods. Both phantoms were placed at the COR and common FOV of the hybrid system. SPECT images were acquired using the vertical axis of rotation (VAOR) orbit. A ±4% energy window symmetric about the 140keV photopeak was used. CT images were acquired with a simple circular orbit at a fixed 6.2° polar tilt.

Reconstructions were done using a ray-driven statistical iterative ordered reconstruction algorithm (ordered subsets expectation maximization (OSEM) for SPECT and ordered subsets transmission (OSTR) for CT). SPECT reconstruction parameters were set to 10 iterations, 8 subsets, 160x160x160 reconstruction grid, and 2.5mm^3 voxel size. CT reconstruction parameters were set to 5 iterations, 16 subsets, 350x350x384 reconstruction grid, and 508μm^3 voxel size. SPECT and CT image sets were registered and fused using an open source *AMIDE* software [25, 26].

e. Breast Phantom

To test image registration and fusion capabilities using non-geometric shapes, images of a 900mL water-filled breast phantom with three lesions (2.7cm, 1.6cm, and 0.8cm diameter) and various sized plastic pieces that simulate non-uniform uptake in the breast background were acquired on the hybrid system. Each lesion was filled with the SPECT radionuclide molecule, aqueous ^{99m}Tc-pertechnetate, (20μCi/mL (0.74MBq/mL) in each lesion) and CT contrast agent (~50μL), Gastrografin with iodine (I_2). The lesion:background radioactive concentration ratio was 10:1. Small and fixed external fiducial markers were used in order to ensure proper registration, be visible and distinguished in both systems, and not interfere with the images. After testing different types of homemade and commercial fiducial markers, four 6.0mm nylon balls (*Small Parts, Inc.* Miami Lakes, FL) soaked in aqueous ^{99m}Tc-pertechnetate were used as markers and taped to the exterior surface of the breast phantom. SPECT images were acquired using a complex acquisition trajectory, three-lobed sinusoid projected onto a hemisphere (PROJSINE) with polar tilting range (sinusodial amplitude) from 15 to 45°, and CT images were acquired using a fixed 6.2° tilt. A ±4% energy window symmetric about the 140keV photopeak was used for the SPECT projections.

SPECT reconstruction parameters were set to 2 iterations, 8 subsets, 150x150x150 reconstruction grid, and 2.5mm^3 voxel size. CT reconstruction parameters remained as previously stated. SPECT and CT image sets were registered and

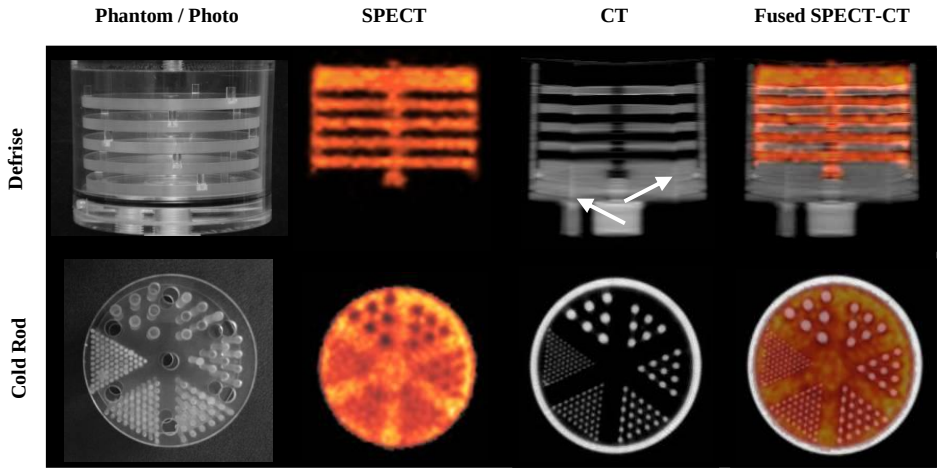

Fig 2: Reconstructed images of the geometric mini-Defrise (TOP ROW) and mini-cold rod (BOTTOM ROW) phantoms were acquired on the hybrid gantry to study the sampling and resolution properties, respectively. CT reconstructed images show slight distortion toward the edges of the mini-Defrise phantom and a circular ring artifact (shown by arrows).

fused using *AMIDE*.

f. Patient Study

Two subject volunteers with confirmed breast cancer were imaged under a protocol approved by the Duke University Medical Center institutional review board (IRB). Informed written consent was obtained from both subjects.

The first subject study was imaged with only the independent, dedicated breast SPECT system using an initial prototype, radiolucent bed lined with lead and foam. This bed was modified with a cutout on the side for the patient's left breast. The subject was a 55yr old, post-menopausal, 59kg woman with biopsy confirmed adenocarcinoma (T2N0). She was injected with 17.8mCi (660MBq) of ^{99m}Tc-sestamibi, which has been shown to accumulate selectively in breast malignancies [27], and scanned using a 45º tilted circular orbit.

The second patient study was done with the hybrid system and the customized patient bed. She was a 45yr old, 93kg patient also with biopsy confirmed breast cancer. Three hours before the hybrid scan, she had received an injection of 29mCi (1073MBq) ^{99m}Tc-methylene diphosphanate (MDP) for a bone scan. While ^{99m}Tc-MDP is used to detect bone metastases, it has much less accumulation in soft tissue tumors, and has been used in early scintimammography studies [28]. However to minimize radiation dose to the patient, the patient was not injected with ^{99m}Tc-sestamibi for the hybrid scan. Four fiducial markers (i.e. nylon balls) were taped to her left breast at 3, 6, 9, and 12 o'clock position. The positioning system of the bed allowed compensation for the bowing of the bed due to the subject's weight. This was done by angling the bed upward and bringing the bed down as far as it could go without hitting the CT tube. In addition, the inner trough of the patient bed was removed to allow more of the breast to protrude into the FOV due to the larger hole in the table and the weight of the patient. The neoprene lining gave additional support and comfort to the subject. After the breast was positioned in the COR of the hybrid system, an 11 minute 360° CT scan was acquired. The patient got up, readjusted herself back on the bed, and a 10 minute SPECT scan using a PROJSINE 15-45° trajectory was performed. This procedure was repeated for the right breast, but the SPECT scan was acquired using a fixed 45º tilted circular trajectory.

Both patients were centered using a vertical beam of a positioning laser which was aligned to the COR of the system. Acquisition trajectories were specifically constructed for the SPECT system to contour each individual breast by measuring the radius of rotation between the camera and breast at six different azimuthal positions and interpolating

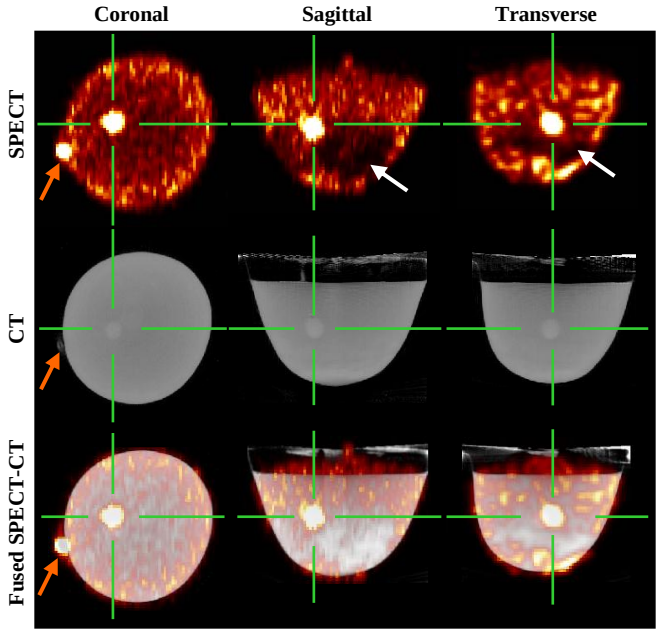

Fig. 3: Reconstructed (TOP) SPECT, (MIDDLE) CT, and (BOTTOM) fused images of a 900mL water-filled breast phantom. The 2.7cm diameter lesion is centered by the green hash marks. Fiducial markers (i.e. nylon balls) were taped to the exterior surface of the breast phantom (orange arrow). Areas with the plastic pieces can be seen as cold spots on the SPECT images (white arrows). The two 3D reconstructed data sets were registered using the fiducial markers.

other RORs about the breast. Reconstruction parameters were the same as used for the breast phantoms.

g. Sampling and Resolution Properties

The reconstructed SPECT, CT, and fused images of the mini-Defrise phantom are shown in Fig. 2 (TOP). As expected, the SPECT reconstructed images acquired using VAOR has sufficient sampling so all four regions between the discs can be clearly seen without any image distortion. The CT reconstructed images, on the other hand, showed slight distortion toward the edges and a circular ring artifact which possibly results from insufficient sampling due to the tilted and offset geometry, respectively. Corrections for these distortions and artifacts are currently being explored. Despite the sampling insufficiency in the CT image, data was registered using common features in both data sets. It would be more useful to have landmark points, such as external fiducial markers, to obtain the necessary registration accuracy between SPECT and CT images rather than the internal ones used here.

Fig. 2 (BOTTOM) shows the reconstructed images obtained of the mini-cold rod phantom. In the SPECT reconstructed images, the first and second largest sectors of rods (4.7 and 3.9mm, respectively) are clearly distinguishable while the third sector of rods (3.1mm) is nearly distinguishable. In the CT images, all six sectors of rods are clearly resolved. Using the rods in the largest sector as internal fiducial markers, the two image data sets were easily registered.

h. Breast Phantom Measurements

Fig. 3 shows the SPECT, CT, and fused reconstructed images. With the help of the fiducial markers, the images from both systems were fused. CT contrast agent was not added to the solution when preparing the fiducial markers since there was enough natural contrast between air and nylon to discriminate them in the projections and reconstructed images (Fig. 3, MIDDLE LEFT). In volumetric 3D space, the SPECT reconstructed images were rotated 90° azimuthally (due to the position of the SPECT system with respect to the CT system) and shifted downward (due to the different bed positions used for SPECT and CT acquisitions). Fiducial markers made it possible to accurately perform these tasks so that the two data sets were aligned as close as possible. As seen in Fig. 3, the location of the plastic pieces are more easily seen in the SPECT reconstructed images as cold spots. However, due to similar attenuation coefficient values between plastic and water, a very narrow window was needed to visualize the plastic pieces in the reconstructed CT slices. This shows the importance of being able to use the anatomical information from CT to guide the localization of suspicious foci seen in SPECT images.

i. SPECT Patient Study

Results of our first SPECT patient study are shown in Fig. 4. There was a clear signal enhancing ~2cm diameter, detailed volume of tracer anterior to the chest wall which corresponded to that seen in the contrast enhanced MRI scan performed earlier in the day. While out of field background activity was minimized due to the use of a radio-opaque pre-prototype bed, streak artifacts and additional enhancing regions that appear in the bottom left of the coronal view and upper left of the transverse view were probably due to the cardiac-hepatic uptake of the radiotracer. Shape distortions were partially due to the incomplete sampling of the tilted parallel beam acquisition orbit, which are consistent with our previously published results on breast phantoms.

j. Hybrid Patient Study

Fig. 5 shows the results of our first hybrid subject study. The images were not fused since the fiducial markers moved during the subject's readjustment between scans. The SPECT breast scan showed very little uptake of the tracer due to its low accumulation in tumors and soft tissue, and the radioactive decay between the times of the bone and SPECT scan. However, in the CT images there were a couple of regions in her left breast which corresponded to known, biopsy confirmed lesions. Previous studies have shown that cancerous tissue has a slightly higher attenuation coefficient than normal breast tissue [20]. The use of a quasi-monochromatic source allows us to be able to differentiate small differences between tissues with similar attenuation values. Attenuation coefficient values were measured by taking an average of the measured mean value in ten different ROIs in the normal glandular and suspected cancerous areas. The measured average attenuation coefficient values in the lesions were $0.296cm^{-1}$ and $0.295cm^{-1}$ in CT Slice #1 and #2, respectively, while the average value in the normal tissue was $0.277cm^{-1}$. This gives a 6.9% and 6.7% contrast difference. Previous studies have reported slightly higher attenuation coefficient values in normal and cancerous tissue for monoenergetic x-ray sources [20]. Some reasons for this slight discrepancy include the use of an x-ray source that is not 100% monochromatic and no implementation of scatter correction in the images. Scatter correction techniques are currently being investigated.

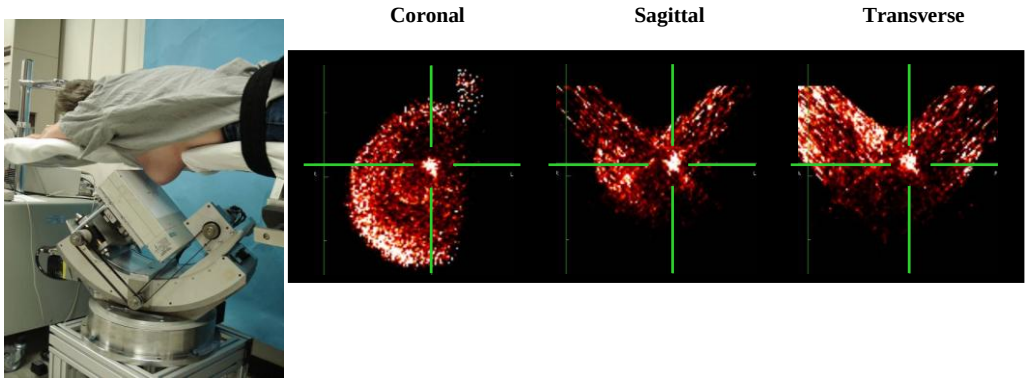

Fig 4: (FAR LEFT) Photograph of the subject on the preprototype bed, suspended over the dedicated breast SPECT system. (RIGHT IMAGES) Reconstructed images of the breast are in coronal, sagittal, and transverse views. Confirmed lesion on the subject's anterior chest wall is indicated at the intersection of the green hash marks

Similar results are shown for the right breast (Fig. 6). The SPECT scan again showed no signs of lesion radiotracer uptake, but the CT scan showed a suspicious lesion with a measured average attenuation coefficient of 0.291cm^{-1} compared to the 0.272cm^{-1} value of the surrounding tissue resulting in a 7.1% contrast difference.

CONCLUSION

Advantages of this dedicated dual-modality SPECT-CT breast imaging tomographic system include: (1) volumetric fully-3D whole breast imaging, (2) registration of complementary functional and anatomical images to further enhance quantitative and visual information, (3) SPECT imaging capability nearly completely contouring the breast, axilla, and with views into the chest wall, (4) lower CT x-ray dose to the breast compared to standard dual-view screening mammography, and (5) acquisition of both SPECT and CT images without moving the patient. Complex 3D acquisition trajectories with the SPECT system are useful to avoid physical hindrances, overcome distortions due to inadequate sampling, and allow detection of lesions in the chest wall and axilla that are not visible using simple circular acquisition trajectories. With the offset geometry, the CT system can image a wide range of breast sizes without truncation artifacts, although other imaging artifacts including the circular ring are still present. Methods to remove these imaging artifacts are being studied.

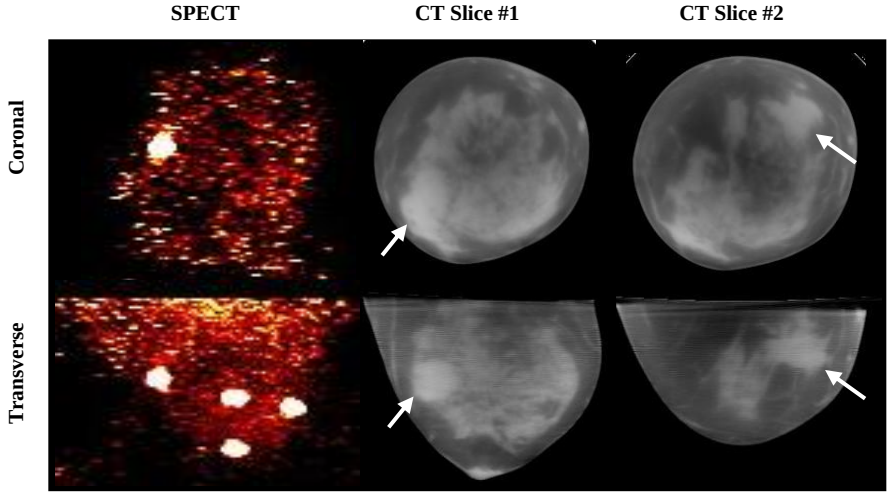

Fig 5: Reconstructed images of the (LEFT) SPECT (shown as a MIP image), (MIDDLE) CT Slice #1, and (RIGHT) CT Slice #2 of the left breast. Although there was no visible tumor uptake of the radiotracer in the SPECT image, there were two suspected lesions seen in the CT images (shown by white arrow). The bright white spots on the SPECT images are the fiducial markers seen in the MIP images.

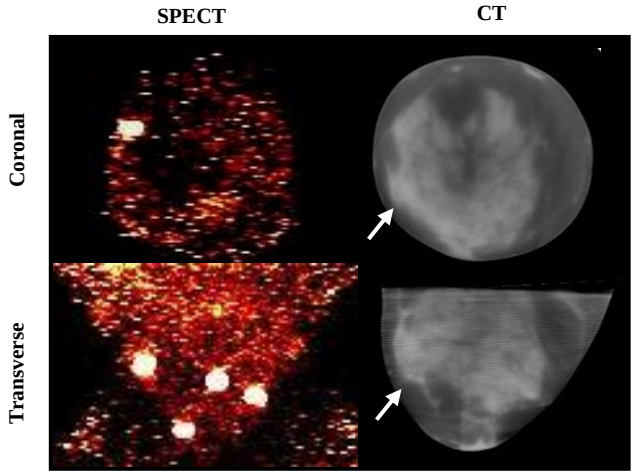

Fig 6: Reconstructed images of the (LEFT) SPECT (shown as a MIP image) and (RIGHT) CT slice of the right breast. Although there was no visible uptake of the radiotracer in the SPECT image, there was one suspected lesion seen in the CT images (shown by white arrow). The bright white spots on the SPECT images are the fiducial markers.

Initial SPECT and hybrid patient study shows promising 3D results. Although the SPECT images can see up to the chest wall, there is limited visualization of the chest wall in the CT system, which remains an important consideration in planned refinements of the current hybrid system. The physical limitations of the system prevent the breast from being positioned farther into the common FOV; however, the five degrees of freedom in bed movement, replacement of the inner trough with flexible material, and more practice with positioning the patient will hopefully allow the chest wall to be imaged. Patient feedback on the comfort of our patient bed will help us improve future iterations. Further hybrid patient studies are still in progress. We believe that the fused images may provide valuable clinical information for more precise detection, staging, and therapy monitoring of cancerous diseases than independent systems alone.

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The authors would like to acknowledge several past and ongoing contributions from James Bowsher. Martin Tornai is the inventor of this technology, and is named as an inventor on the patent for this technology applied for by Duke. If this technology becomes commercially successful, Martin Tornai and Duke could benefit financially.

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